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Mixed Nucleobase Complexes *cis*-$Pt(NH_3)_2TX$ with T = 1-Methylthymine Anion and X = 1-Methylcytosine, 9-Ethylguanine, 9-Methyladenine and 9-Methyladeninium Cation

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The preparation is described of possible cross-linking products of cis-*Pt(II) with the 1-methylthymine anion T as one base, and 1-methylcytosine C, 9-ethylguanine G, and 9-methyladenine A, respectively, as the second base.* ^1H *NMR spectra are used to assign the donor atoms of the nucleobases in these complexes: T in all cases is bound to Pt through N3, C through N3, G through N7, and with A through N7 (monodentate), N1 (monodentate), and N7, N1 (bridging). Protonation of* cis-$[Pt(NH_3)_2T(A\text{-}N^7)]^+$ *gives* cis-$[Pt(NH_3)_2T(HA\text{-}N^7)]^{2+}$*, a complex containing a protonated A ligand. Warming of this complex leads to a H transfer from HA to T and subsequent elimination of neutral HT. This occurs both in* H_2O *and* Me_2SO *as solvents. With* Me_2SO*, in a secondary reaction,* NH_3 *is released from the complex and deprotonates the still available HA ligand eventually giving* NH_4^+*.*

Introduction**

It is generally assumed that the antitumor agent *cis*-$Pt(NH_3)_2Cl_2$ acts through a bifunctional attack on DNA nucleobases with replacement of the chloro ligands [1]. Interaction with DNA appears to be rather complex [2], with a variety of reaction products theoretically possible [3]. The question concerning *the* important reaction(s) with regard to the antitumor activity of *cis*-Pt(II) has not been settled yet, even though there are now strong indications on a specific reaction with oligo(dG)·oligo(dC) sequences [4, 5], verifying earlier findings on a preferential reaction of Pt compounds with GC-rich DNAs [6–9]. This suggests that GG, GC, or CC complexes may be of particular relevance for the action of *cis*-Pt(II) as an antitumor agent.

In an attempt to systematically synthesize and study complexes of *cis*-Pt(II) with model nucleobases, we have so far concentrated primarily on complexes of C [10], mixed GC complexes [11], and complexes of T and U [12]. We herewith report on mixed nucleobase complexes of *cis*-$Pt(NH_3)_2^{2+}$ containing the anion of 1-methylthymine, T, as one base and C, G, A, and HA as second nucleobase, *viz.* *cis*-$[Pt(NH_3)_2TC]^+$, *cis*-$[Pt(NH_3)_2TG]^+$, *cis*-$[Pt(NH_3)_2TA]^+$, and *cis*-$[Pt(NH_3)_2T(HA)]^{2+}$. Preparation of these complexes has been achieved via the recently described *cis*-$Pt(NH_3)_2T\,Cl$ complex [12c]. Attempts to synthesize the above mixed nucleobase complexes by an alternative route, *e.g.* by first coordinating C, G, or A and subsequently T, were unsuccessful or gave the desired products in very low yield only.

Of particular interest in this study was the site of Pt coordination with 9-methyladenine, with this ligand having at least two sites of good basicity, N1 and N7 [13].

Experimental

9-Methyladenine was prepared through reaction of adenine (Sigma) with CH_3I/KOH according to the published procedure [14]. The product obtained was identical with that purchased from Vega Biochemicals. Deuterated 9-methyladenine (ND_2, C(8)D) was obtained by 8 h heating (80 °C) in excess D_2O and crystallization from D_2O.

cis-$Pt(NH_3)_2TCl\cdot H_2O$ was prepared as previously described [12c]. The mixed ligand complexes were prepared by reaction of $Pt(NH_3)_2TCl\cdot H_2O$ with 1 equiv. of AgX (X = NO_3^-, ClO_4^-) and subsequent addition of the second nucleobase ($c_{Pt} \cong 5 \times 10^{-2}$ *M*, H_2O. 40 °C, 24 h). The compounds were obtained after filtration of AgCl and concentration of the filtrate. No attempts were made to optimize the yields. *cis*-$[Pt(NH_3)_2TC]NO_3\cdot 3H_2O$, *1*: Yield 30%. Colorless, transparent cubes. *Anal. Found: C, 21.85*; H,

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**Abbreviations used: T = 1-methylthymine anion; HT = 1-methylthymine; C = 1-methylcytosine; G = 9-ethylguanine; A = 9-methyladenine; HA = 9-methyladeninium cation, U = 1-methyluracil anion. Occasionally C and G are used to indicate nucleotides (introduction). A-N^7 means A coordinated to Pt via N7 *etc.*

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4.35; N, 18.17; Pt, 32.3; Calcd. for $Pt(NH_3)_2(C_6H_7N_2O_2)(C_5H_7N_3O)NO_3 \cdot 3H_2O$: C, 21.67; H, 4.31; N, 18.39; Pt, 32.01.

cis-$[Pt(NH_3)_2TG]ClO_4 \cdot 2H_2O$, *2*: The NO_3^- salt (85% yield) was recrystallized from an aqueous $NaClO_4$ solution. Yield of 1st fraction 45%. Colorless, transparent nuggets. *Anal.* Found: C, 22.56; H, 3.91; N, 18.71; Calcd. For $Pt(NH_3)_2(_6H_7N_2O_2)(C_7H_9N_5O)ClO_4 \cdot 2H_2O$: C, 22.86; H, 3.84; N, 18.46.

cis-$[Pt(NH_3)_2T\ (A\text{-}N^7)]ClO_4 \cdot 0.5H_2O$, *3*: The compound crystallized from an aqueous solution (pH = 6) upon slow evaporation to $c_{Pt} \cong 0.15$ *M*. Yield 45%. Colorless, transparent cubes. *Anal.* Found: C, 22.98; H, 3.35; N, 20.41; Calcd. for $Pt(NH_3)_2(C_5H_7N_2O_2)(C_6H_7N_5)ClO_4 \cdot 1H_2O$: C, 22.99; H, 3.22; N, 20.12.

The concentrated filtrate was then passed over Sephadex G10 and eluted by H_2O. In sequence of their appearance the following components were obtained: *cis*-$[(NH_3)_2TPtAPtT(NH_3)_2](ClO_4)_2 \cdot 2H_2O$, *4* (yield 15%), *cis*-$[Pt(NH_3)_2T(A\text{-}N1)]ClO_4$, *5* (yield 15%), unreacted A, and an unidentified T complex, *6* (yield estimated 5%). Only *3* and *4* were obtained analytically pure, whereas *5* and *6* always were contaminated with A.

cis-$[(NH_3)_2TPt(A\text{-}N^7,N^1)PtT(NH_3)_2](ClO_4)_2 \cdot 2H_2O$, *4*: In an alternative way, *4* was prepared by direct reaction of *3* with *cis*-$[Pt(NH_3)_2T(H_2O)]ClO_4$ (0.1 *M* Pt, 76 h, 40 °C). Upon slow evaporation at 22 °C and filtration of unreacted *3*, compound *4* was obtained in 30% yield as yellow powder. *Anal.* Found: C, 19.36; H, 3.53; N, 16.22; Cl, 5.89. Calcd. for $[(NH_3)_4Pt_2(C_6H_7N_5)(C_6H_7N_2O_2)](ClO_4)_2 \cdot 2H_2O$: C, 19.29; H, 3.34; N, 16.24; Cl, 6.3.

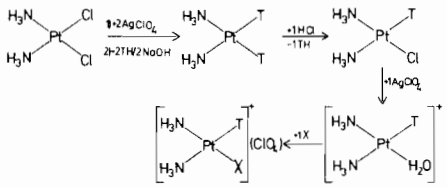
cis-$[(NH_3)_2PtT(HA\text{-}N^7)](ClO_4)_2 \cdot 1H_2O$, 7: 0.5 mmol *3* were dissolved in 20 ml H_2O, filtered, and 1.3 ml 0.4 *N* HNO_3 and 150 mg $NaClO_4 \cdot H_2O$ were added. Slow evaporation gave 200 mg of *7* (55% yield) as colorless crystals. *Anal.* Found: C, 19.26; H, 3.25; N, 17.14; Calcd. for $(NH_3)_2Pt(C_6H_7N_2O_2)(C_6H_8N_5)(ClO_4)_2 \cdot H_2O$: C, 19.59; H, 3.16; N, 17.13.

^1H NMR spectra (concentrations *ca.* 0.1 *M* Pt) were recorded on a Jeol JNM-FX 60 Fourier-transform spectrometer at 30 °C. An average of 1000 transients were accumulated into 8 K data points of memory. Chemical shifts are given on the δ scale. In $Me_2SO\text{-}d_6$ shifts were referenced to internal tetramethylsilane, TMS, in D_2O an internal $[N(CH_3)_4]BF_4$ reference was used and shifts were calculated to Sodium 3-(trimethylsilyl)propanesulfonate, TSP, (−3.1869 ppm relative to $N(CH_3)_4^+$). pD values were obtained by adding 0.4 units to the obtained pH meter reading. $Me_2SO\text{-}d_6$ was stored over 4 Å molecular sieves. With dried samples, molecular sieves had been added to the sample and removed prior to recording the spectra. Attempts to remove water from samples containing protonated HA ligands by this method were unsuccessful and resulted in formation of the corresponding complex with the neutral A ligand. This was a consequence of the reaction of zeolites with H_2O leading to formation of base which then neutralizes the HA ligand. (*cf.* also ref. 11b).

Results and Discussion

TC, TG, TA Complexes

The described complexes were obtained via the following route:



with X = C, G, A.

Chemical shifts of the individual ^1H-resonances of the prepared compounds in $Me_2SO\text{-}d_6$ are listed and assigned in Table I. Removal of water of crystallization from the solution by means of molecular sieves does not cause appreciable shifts of the proton signals. In all compounds, T is bound to Pt through the deprotonated N3 position, as expected from the way of preparation and consistent with the ^1H NMR shifts [12c]. C is bound to the Pt through N3 as well, as indicated by $^{195}Pt-^1H(5)$ coupling ($^4J \cong 15$ Hz), G through N7 (^{195}Pt coupling with $^1H(8)$: $^3J \cong 24.6$ Hz). Chemical shifts of C and G ligands are close to those reported by us previously for related complexes [10a,d,f; 11b] with X-ray crystallographically confirmed binding sites.

Reaction of *cis*-$[(NH_3)_2PtT(H_2O)]^+$ with A (1:1) gave at least four products, two of which were isolated in analytically pure form as perchlorate salts: $[Pt(NH_3)_2T(A\text{-}N^7)]^+$, *3*, and $[(NH_3)_2TPt(A\text{-}N^7,N^1)PtT(NH_3)_2]^{2+}$, 4. A third compound, most likely $[(NH_3)_2PtT(A\text{-}N^1)]^+$, *5*, and a fourth, T containing complex *6* were isolated as well but were contaminated with unreacted A. Formation of both N7 and N1 bound A complexes had been expected on the basis of earlier solution studies on the reaction of dien Pt(II) [15, 16] and dien Pd(II) [16] with adenosine, which yielded a mixture of complexes with unidentate binding via N1 and N7 and bridging through N1, N7. This appears to be a consequence of the rather similar nucleophilicities of N1 and N7 sites of A for Pt. Only in moderate to strongly acidic medium does N1 become less available as a metal coordination site, due to protonation (estimated pK for protonation of A is 3–4, similar to adenosine [17]), and N7 metal binding is increasingly favoured. Assignments of A binding sites have been achieved by the use of A deuterated at the C8 position; with

TABLE I. ^{1}H NMR Shifts (δ, ppm) and Coupling Constants J (Hz) of Mixed TX Complexes in Me_2SO-d_6 (30 °C, 0.1 *M* Pt).

	T			C						
	H6	N-CH_3	C-CH_3	NH_2	H6	H5	N-CH_3		NH_3	H_2O
cis-[$Pt(NH_3)_2$TC]NO_3 aq., *1*	7.257	3.158	1.704	9.071 8.344	7.684 J_{H-H} = 7.1	7.751 J_{H-H} = 7.1 J_{Pt-H} = 14	3.285		4.172 4.106 J_{Pt-H} = 50	3.363
	T			G						
				NH	H8	NH_2	$-CH_2-$	CH_3		
cis-[$Pt(NH_3)_2$TG]ClO_4 aq., *2*	7.230 $J \sim 0.9$	3.158	1.692 $J \sim 0.9$	11.269	8.135 J_{Pt-H} = 24.6	6.844	4.033 J_{H-H} = 7.2	1.250 J_{H-H} = 7.2	4.327 4.205 J_{Pt-H} = 50	3.350
	T			A						
				H8	H2	NH_2	N-CH_3			
cis-[$Pt(NH_3)_2$T(A-N^7)]ClO_4 aq., *3*	7.212	3.150	1.696	8.613 J_{Pt-H} = 24	8.254	8.409	3.816		4.225 3.984 J_{Pt-H} = 50	3.330
cis-[$(NH_3)_2$TPtAPtT$(NH_3)_2$]$(ClO_4)_2$ aq., *4*	7.212	3.203 3.163	1.749 1.696	8.777		9.65	3.849		4.303 4.135 J_{Pt-H} = 50	3.367
cis-[$Pt(NH_3)_2$T(A-N^1)]ClO_4 aq., *5*	7.212	3.158	1.708	8.217	8.646	8.60	3.731		4.221 J_{Pt-H} = 50	3.330

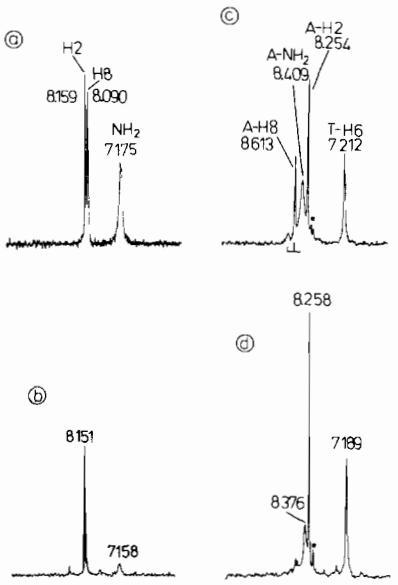


Fig 1. Lowfield portion of ^{1}H NMR spectra (Me_2SO-d_6). a) A; b) deuterated A (ND_2, C(8)D), c) *cis*-[$(NH_3)_2$Pt T (A-N^7)]ClO_4, *3*, d) deuterated *3* (A. ND_2, C(8)D); * in spectra c), d) denoted contamination with A.

H8 of A exchanging rapidly for ^{2}D in D_2O [18], not only is an assignment of H2 and H8 resonances in the free ligand possible but also, because of ^{195}Pt coupling with ^{1}H(8) in the case of N7 binding or ^{1}H(2) with N1 binding, in the Pt complexes (Fig. 1). In the free ligand H8 appears at higher field than H2, similar to the situation with unsubstituted adenine [18] and 9-ethyladenine at 30 °C [19], but different from adenosine [20] with reversed positions of these two resonances.

There is a striking variability in the positions of H2 and H8 resonances of A depending upon the solvent and, to a smaller extent, on the neighbouring ligands. For example, [$(NH_3)_2$PtT(A-N^7)]$^+$ exhibits its H2 and H8 resonances at 8.254 and 8.613 ppm, respectively, in Me_2SO (c = 0.1 *M*), but at 8.266 and 8.478 ppm in D_2O (pD = 6, c = 0.07 *M*). If T is replaced by C, *cis*-[Pt$(NH_3)_2$C(A-N^7)]$^{2+}$*, resonances are observed at 8.307 (H2) and 8.870 (H8) ppm in Me_2SO, yet at 8.327 and 8.543 ppm in D_2O (pD = 7.3) at identical concentrations (0.07 *M*). Even through ^{1}H resonances are known to be sensitive towards changes in the environment, with T complexes (N3 bound to Pt) the H5 resonance occurs in a much narrower range, 7.24 ± 0.02 ppm ([12c] and Table I), and the same applies for the H8 resonance of different G complexes with N7 platinum binding, 8.15 ± 0.05 ppm ([10f, 11b] and Table I).

*N7 coordination has been verified by X-ray analysis (to be published).

Similar variations in H2 and H8 resonances of adenosine are evident if one compares the reported shifts of a variety of its complexes with Pt and Pd, either in identical or different solvents [21].

9-Methyladenine binding through N1 in *5* is assigned on the basis of the H2 shift in the 8-D adenine complex. As can be seen (Table I), the relative positions of H2 and H8 in *3* and *4* are reversed. There is, admittedly, no unambiguous proof for N1 platinum binding in *5*. N3 coordination might cause a similar shift and an identical ^{195}Pt coupling with H2 as does N1 coordination. However, with no known example of N3 metal binding to a N9 substituted adenine, it appears reasonable to rule out this possibility on steric grounds*. On the other hand, crystallographically confirmed metal binding through N1 only is also rather sparse [23].

The assignment of the A-bridged complex *4* has been verified by direct reaction of isolated *cis*-[Pt-$(NH_3)_2$T(A-N^7)]$^+$ with *cis*-[Pt$(NH_3)_2$T(H_2O)]$^+$. Binding of A occurs through N7, as logical from the way of preparation, and N1, as evident from ^{195}Pt coupling satellites of the H2 resonance in the adenine-D8 form. N1, N7 binding appears to be a rather frequent way of metal coordination of adenine residues, as can be concluded from the number of published structures on such complexes [24–27].

Protonation of the TA Complex, Decomposition and Release of NH_4^+

When $HClO_4$ is added to an aqueous solution of *3*, *cis*-[Pt$(NH_3)_2$T(HA)]$(ClO_4)_2 \cdot 1H_2O$, *7*, is isolated. In its ^{1}H NMR spectra (D_2O and Me_2SO-d_6), a shift of both H2 and H8 resonances of A to lower field is observed, whereas the H6 resonance of T is almost unaffected. A· H8, 8.809; H2, 8.442, CH_3, normal in Me_2SO-d_6, c = 0.1 *M* (*cf.* Table I and see Fig. 2). This indicates protonation at A but not at T. The acidic proton exchanges with A-NH_2 and water of crystallization and leads to an averaged, broad signal of the expected intensity around 5.4 ppm. Warming of a D_2O sample of *7* to 90 °C results in the gradual disappearance of the original signals and in the appearance of sharp signals due to neutral 1-methylthymine, HT, and a series of unresolved signals assigned to adenine complexes (*vide infra*). Within 3 h at 90 °C, 90% of the original T ligand has been displaced.

With Me_2SO instead of H_2O, brief heating to 90 °C (10 min) results in dramatic spectral changes (Fig. 2)· not only are there new signals of neutral HT, but also a new triplet of relative intensities 1:1:1 centered at 7.093 ppm (J = 51.5 Hz) which can be unambiguously assigned to NH_4^+. A qualitative test

*It is, however, well established that unsubstituted adenine can bind metals through N3 as well *Cf.* ref. 22.

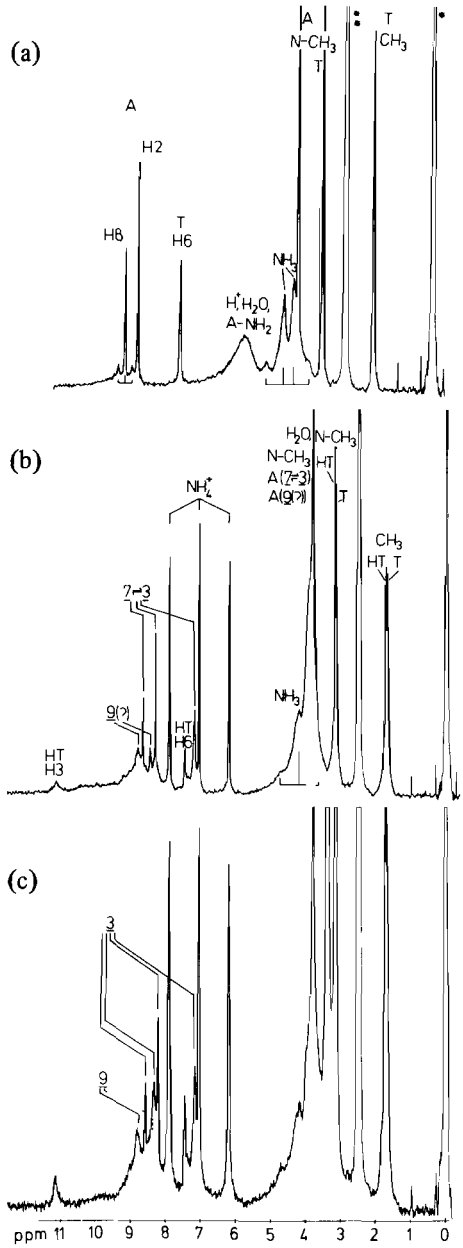
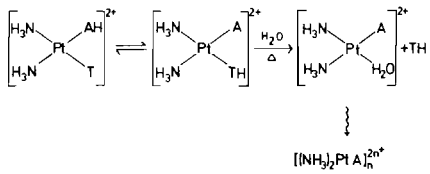


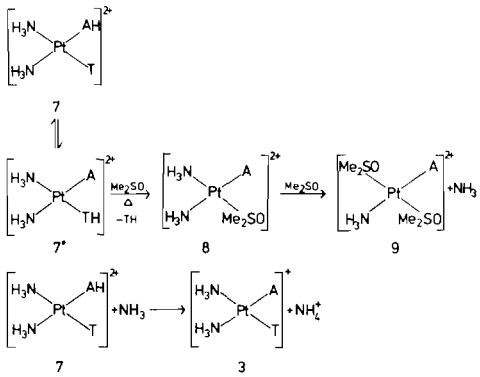
Fig. 2. ^{1}H NMR spectra (Me_2SO-d_6, 0.1 *M* Pt). a) *cis*-$[(NH_3)_2PtT(HA)](ClO_4)_2$, *7*. b) Spectrum after 10 min at 90 °C. c) Spectrum after 30 min at 90 °C. *TMS. **Solvent.

with Nessler's reagent also proves formation of NH_4^+. The original NH_3 signal decreases in intensity, the resonance of T and HA ligands of *7* are shifted and indicate formation of the unprotonated complex *3*. Moreover, there are two new sets of sharp adenine H2 and H8 signals (8.462, 8.487; 8.826, 8.846 ppm) and a very broad one (around 10 ppm), observable after 10 min at 90 °C only, and later on partially buried under the A-NH_2 signal of *3*. It does not become clear from the spectra whether the two sets of sharp signals are due to two species or a single one with two different ligand orientations. The reaction stops after about 30 minutes with the relative intensities of HT and NH_4^+ being roughly equal, unless acidic protons, *e.g.* from 9-methyladeninium perchlorate, are added. The reaction proceeds with formation of HT and NH_4^+. A sample of *7*, heated in H_2O, evaporated to dryness and redissolved in Me_2SO-d_6, does not show any resonances of NH_4^+. Only after *ca.* 15 min at 22 °C do such signals appear.

These findings are interpreted as follows: heating of *cis*-$[Pt(NH_3)_2T(HA)]^{2+}$ in either water or Me_2SO results in the removal of TH from the complex. This indicates a primary proton transfer from the HA ligand to T, since only N3 platinated neutral thymine is readily expelled from Pt complexes [12c].



The mono(9-methyladenine) complex formed undergoes di- or oligomer formation giving rise to the mentioned unresolved signals. Reaction in Me_2SO is qualitatively different from that in water: removal of TH is followed by coordination of Me_2SO and subsequent loss of NH_3 *trans* to Me_2SO. NH_3 eventually is protonated by the still available acidic protons of the HA ligands to give NH_4^+. At most 50% of the HT ligand can thus be replaced and 50% of the originally bound NH_3.



^{1}H NMR spectra agree with the outlined reaction sequence. The fact that somewhat more NH_4^+ (60%) than HT (40%) is formed could be due to a partial isomerization of *trans*-$[Pt(NH_3)_2A(Me_2SO)_2]^{2+}$ *9*, to the corresponding *cis*-product which might lead to further release of NH_3. Similar *trans*–*cis* isomerizations have previously been reported [28]. Intermediate *7* is not observed in the ^{1}H NMR spectrum. As mentioned above, no definite assignment of the

new adenine signals in the spectrum is possible after 10 min 90 °C (Fig. 2b). However, it seems reasonable to assign the signal around 8.83 ppm in the spectrum 2c exclusively to *9* since NH_3 release is virtually complete. The replacement of NH_3 from a *cis*-Pt-$(NH_3)_2^{2+}$ complex is a consequence of the *trans*-effect of Me_2SO. No such reaction is observed in aqueous solution. As previously recognized in related systems, the removal of NH_3 is facilitated by protonation of free NH_3 to give NH_4^+, since this prevents the reverse reaction [29].

The release of NH_3 from *cis*-Pt(II) during its reaction with adenine, reported by Wherland *et al.* [30], certainly cannot occur via an identical pathway, since no Me_2SO was applied. The same is true for suggestions that, with pyrimidine-2,4-diones as ligands, release of NH_3 may occur in aqueous solution [31]. Yet another example of NH_3 release from a *cis*-Pt(II) complex, *cis*-$[Pt(NH_3)_2CCl]Cl$, caused by the *trans*-effect of chloride, has been reported [32] and recently confirmed by us using X-ray crystallography [10b].

Acknowledgements

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